Beyond QT Prolongation in Drug Studies

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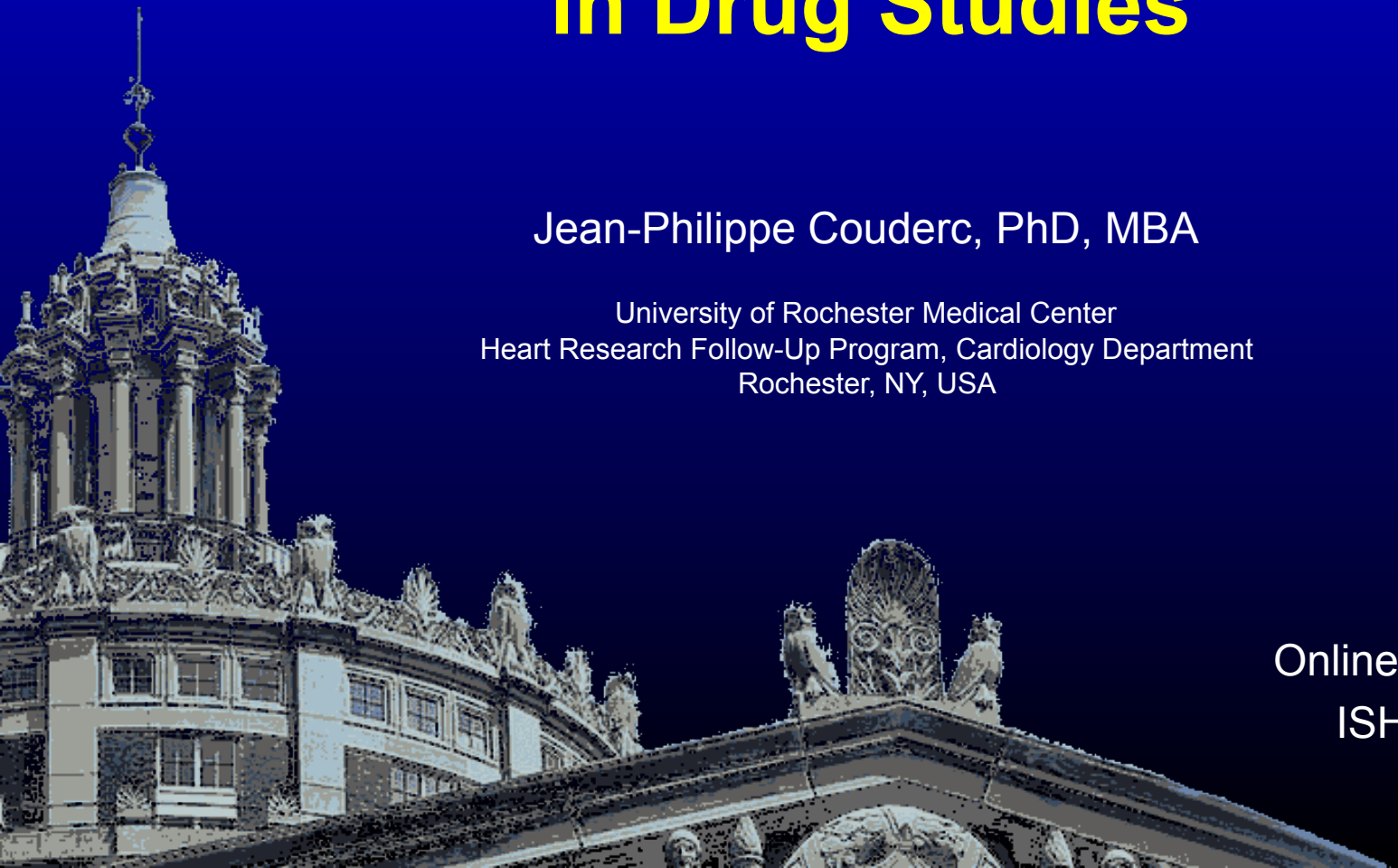


Online Symposium
ISHNE 2007

Background I

- **The acquired form of the Long QT syndrome (LQTS) has been associated with several major drugs that were withdrawn from the market after being associated with numerous arrhythmic events and cardiac death.**
- **Most of these drugs target the HERG leading to a reduction of specific potassium currents in the myocardial cells (I_{Kr})**

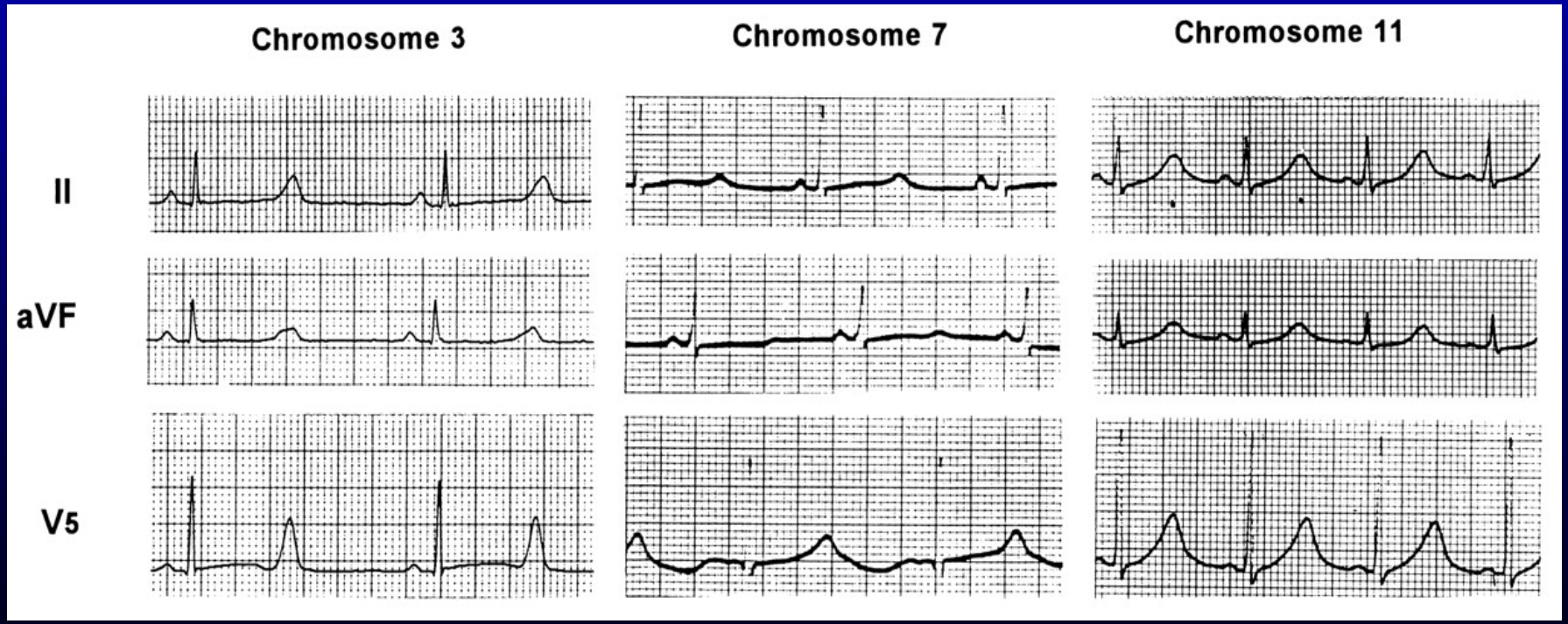
Background II

- **These drugs were also associated with variable prolongation of the QT interval on the surface ECGs revealing one of the limitations of this marker.**
- **Consequently, it is important to design a method for the assessment of drug-induced repolarization cardiotoxicity that**

What Have We learnt from the Congenital LQTS?

T-wave morphology and the congenital LQTS

- **Observations based on 153 families with marker linkage to :**
  - **Chromosome 3 (n=47), chromosome 7 (n=30), and chromosome 11 (n=76)**



Moss AJ, Zareba W, Benhorin J et al. ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation. 1995;92:2929-2934.

Rational
for investigating T-wave morphology

Early diagnosis of LQTS is critical because various prophylactic therapies can effectively reduce the risk for life-threatening arrhythmias. Although genetic testing is the gold standard for verification of the underlying gene abnormality in LQTS patients, it is frequently not accessible (patients' refusal), too expensive, or results could be delayed. Consequently, it is important to assess whether computerized ECG might be helpful in clinical pre-screening (prior to genotyping) of individuals suspected for LQTS. We investigated two specific aims:

Study 1: Can T-wave morphology improve the identification of patients carrier of a LQTS mutation but with a near-normal QT interval duration?

Study 2: Can T-wave morphology discriminate gene-specific syndrome?

Study 1

Repolarization Morphology in LQT2 Patients

Study based on data from the International Registry for the Congenital LQTS

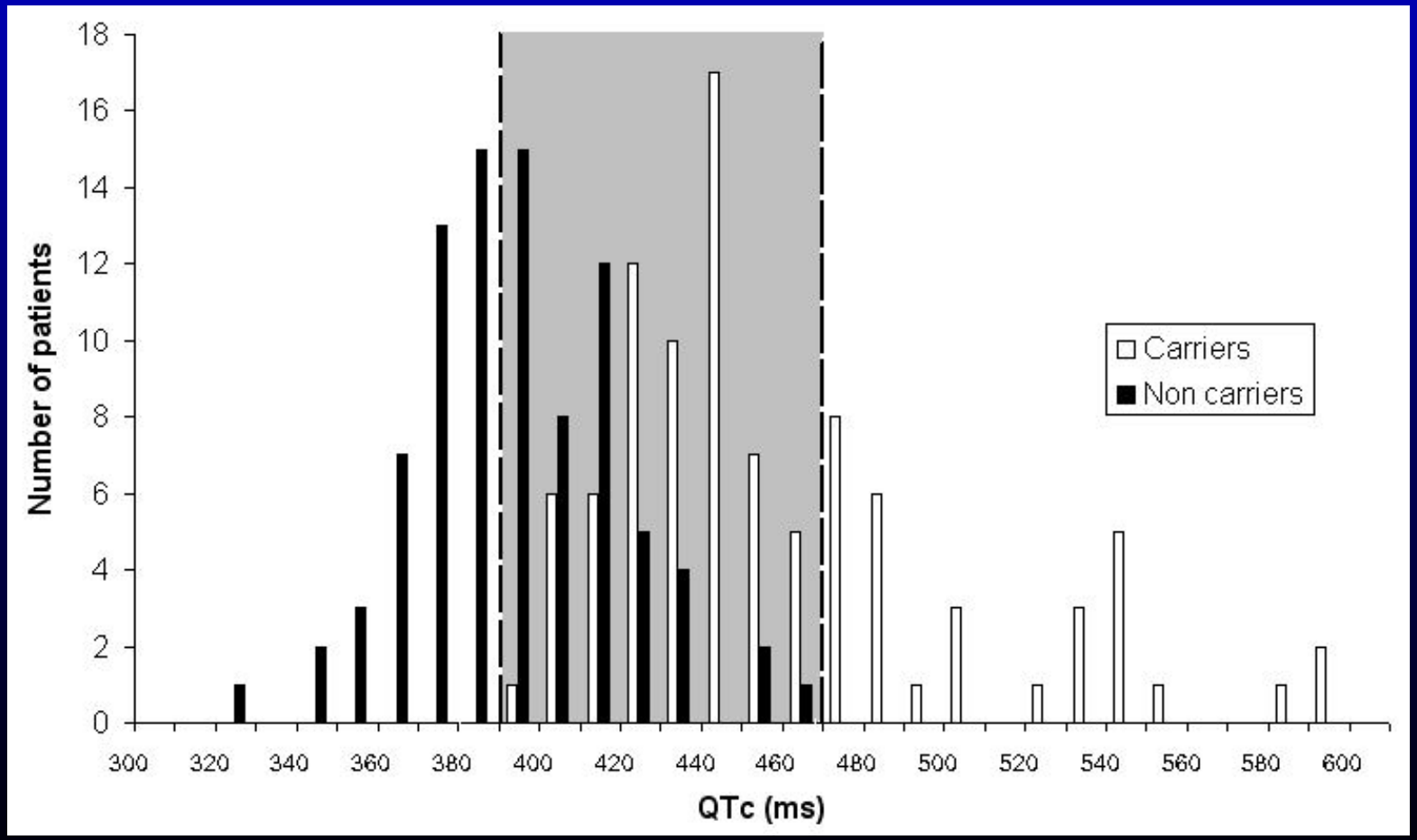
Couderc JP, McNitt S, Xia J, Zareba W, Moss AJ. Repolarization morphology in adult LQT2 carriers with borderline prolonged QTc interval. *Heart Rhythm* 2006 December;3(12):1460-6

Couderc JP, McNitt S, Xia X, Zareba W, Moss A.J. Discrimination of hERG carrier from non-carrier patients with borderline prolonged QTc intervals. Computers in Cardiology, Valencia Spain, IEEE Computers Press, 2005 p. 125-8

Study 1

QTc interval Distribution in LQT2

- **All QTc values (n=159)** * Bazet corrected QT interval
- **Near-normal QTc interval duration (390 to 470 msec, n= 95)**



Study 1

Study Population

	No β-blockers therapy		**No** β-blockers therapy *390≤QTc≤470*	
	Non-carrier	**Carrier**	**Non-carrier**	**Carrier**
N	90	69	46	49
Female (%)	61.1	58.0	78.3	59.2*
Age (yrs)	32.9±14.4	37.8±17.0	32.4±13.8	36.7±16.6
Prior CE	5.6	31.9*	6.5	26.5*
HR (bpm)	71.7±13.8	67.0±12.6*	76.2±13.1	66.7±12.6*

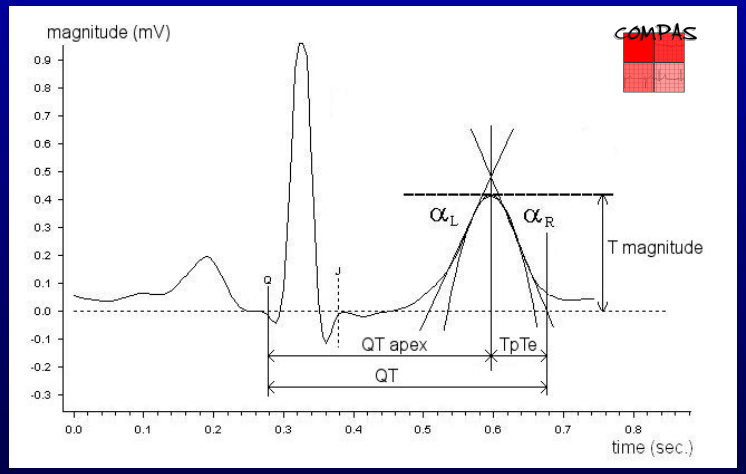
CE: cardiac Event

* p≤0.05, † p≤0.01 comparing non-carrier to carrier groups

Study 1

Repolarization Parameters

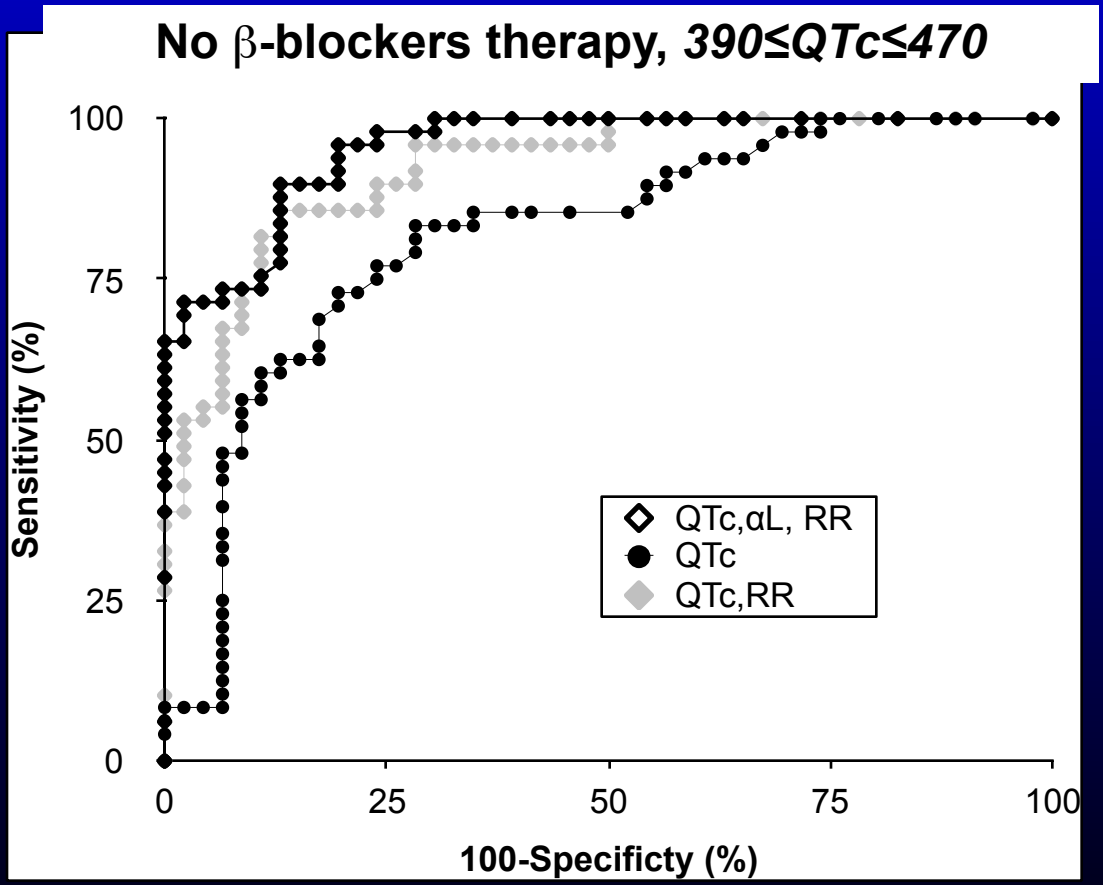
	Non-carrier	Carrier
N	46	49
T magnitude (mV)	0.24±0.12	**0.16±0.07***
QT apex (msec)	293.9±24.5	**336.2±33.6***
QT (msec)	368.9±28.4	**428.1±35.5***
QTc (msec)	412.6±17.7	**435.4±18.6***
RR (msec)	807.1±136.2	**972.7±149.1***
α_R (mV/sample)	-0.017±0.009	**-0.010±0.005***
α_L (mV/sample)	0.013±0.006	**0.006±0.003***
TpTe (msec)	74.7±9.9	**93.0±25.8***
T symmetry	0.80±0.36	0.76±0.38



T Symmetry is the ratio of right to left slope of the T-wave
* $p<0.05$

Study 1

Use of T-wave morphology for identifying carrier from non-carrier individuals



Gender was not retained in the model.

$$\text{Log}(p/(1-p))=-44.0+0.083QTc-0.013RR-318\alpha_L$$

Study 2

T-wave Morphology as a Phenotypic expression of the LQTS

Study based on data from the International Registry for the Congenital LQTS

Vaglio M, Couderc JP, McNitt S, Zareba W, Moss AJ. ECG-based method for identifying kvLQT1/KCNE1 or HERG mutation in patients with the long QT syndrome. Annual Scientific Sessions of the American College of Cardiology February 21st, 2006, Atlanta, GA in JACC Vol. 47 no.4 (Supp A): 13A

Vaglio M, Couderc JP, Xia X, Zareba W. Quantitative Repolarization Patterns Identifying KvLQT1 and KCNH2 Mutation in Patients with the Long QT Syndrome, Heart Rhythm 2007, in press.

Study 2

Study population

	Healthy	LQT1	LQT2
N (females)	38 (29%)	49 (71%) †	25 (76%) †
Age (yrs)	27.5 ± 8.1	34.3 ± 10.2 †	35.5 ± 9.4 †
Betablockers (%)	0	63	44
RR (ms)	767 ± 74	849 ± 110 †	837 ± 134
QT (ms)	360 ± 20	450 ± 38 †	466 ± 70 †
QTc F (ms)	394 ± 16	478 ± 29 †	494 ± 49 †
QTc B (ms)	413 ± 17	493 ± 29 †	510 ± 41 †

Average values and standard deviations for overall diurnal period. Measurements are from lead V5.
QTc B: heart-rate corrected QT using Bazett's formula; QTc F: QTc corrected using Fridericia formula.
†: $p < 0.05$ in comparison to healthy.

Holter ECG Recordings

-Ambulatory Holter ECGs:

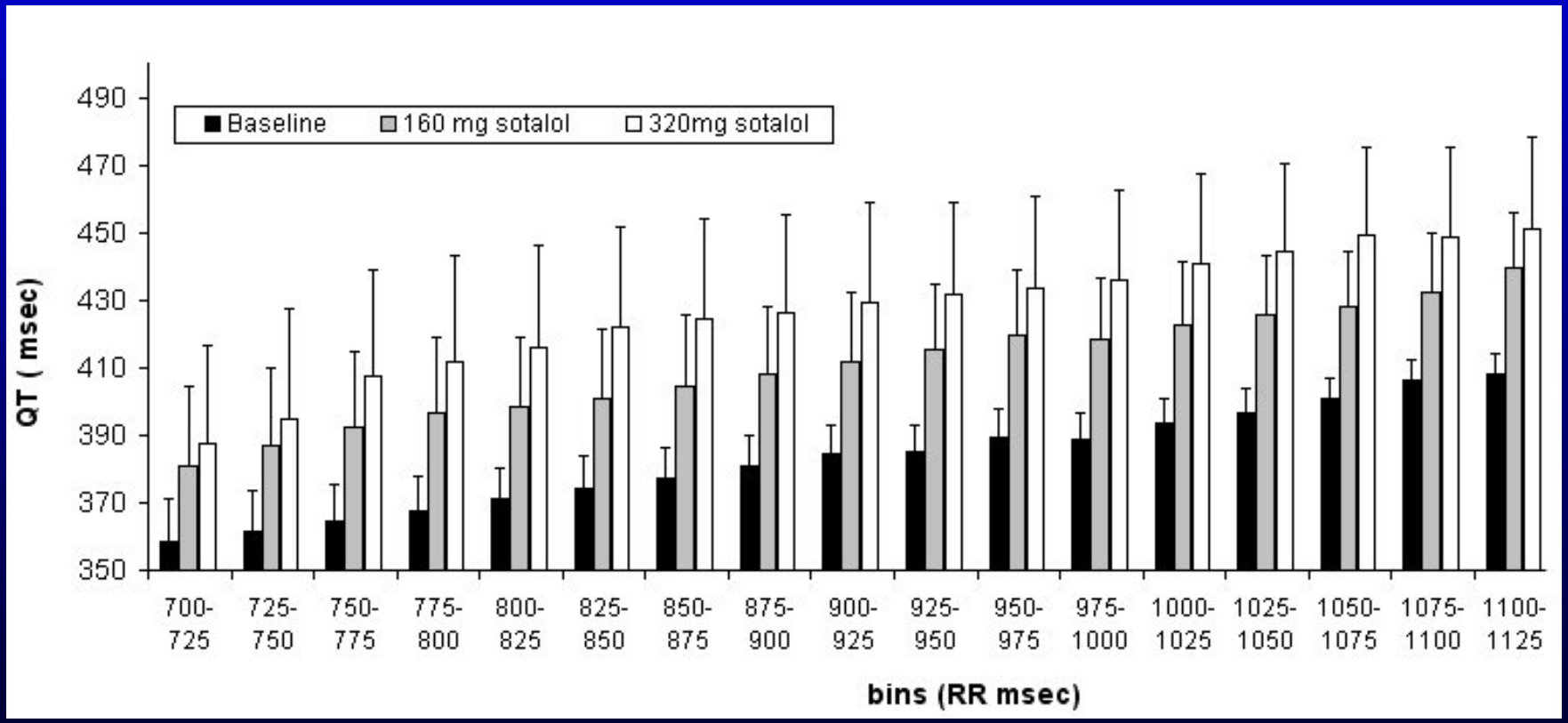
- -Holter H12 recorders providing 12-lead ECG signals (Mortara Instrument, Milwaukee, WI).
- -Amplitude resolution: 12 bits (6.25 μV)
- -Sampling frequency: 180Hz
- -ECG duration : ~24 hours

-Measurement during steady-state repolarization: Representative beats based on 10 consecutive beats.

- -Steady state : $\Delta RR<300$ msec within the preceding 5 minutes.
- -HR stability : $|\Delta RR|<10$ %
- -Exclusion of on-sinus beats

Study 2

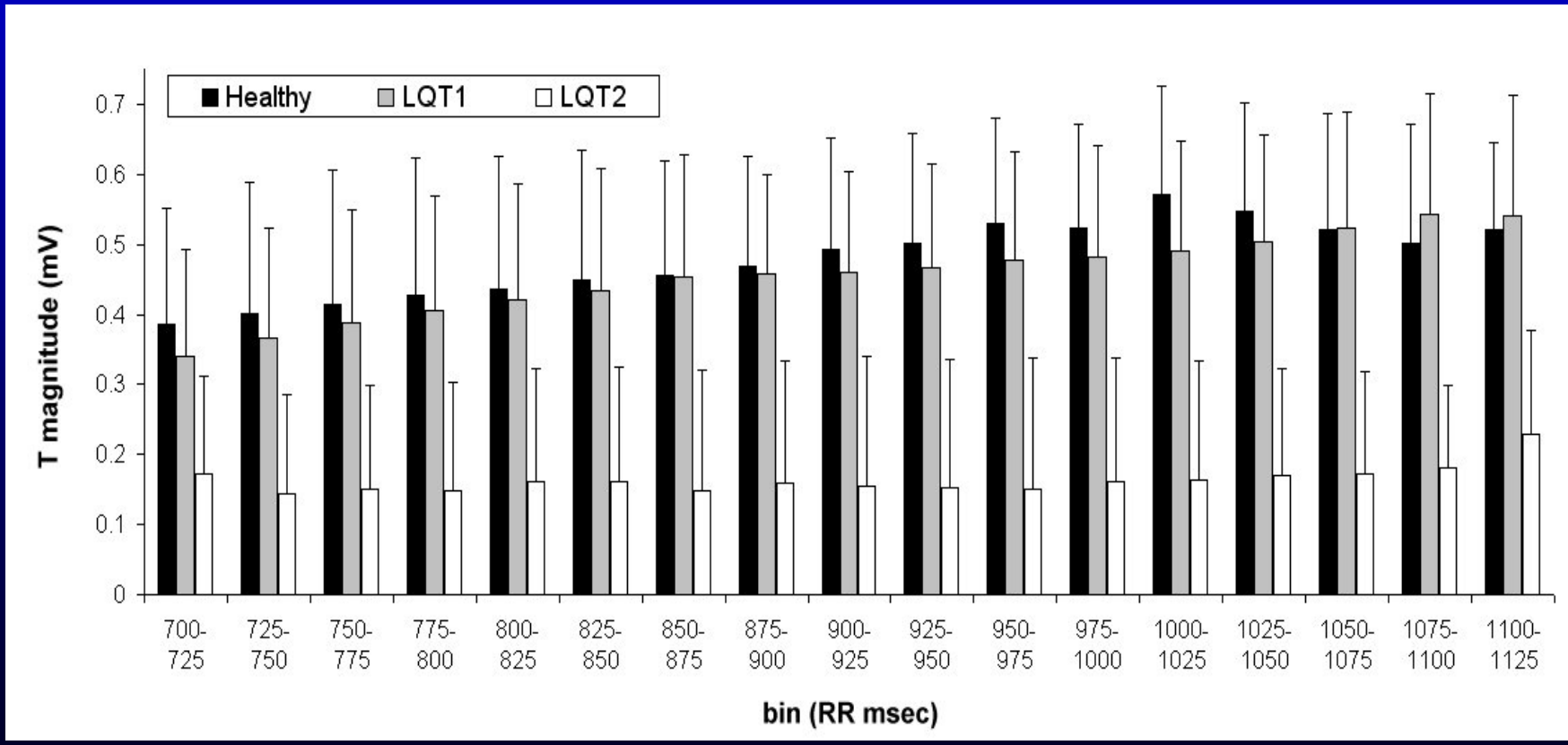
QT Interval Prolongation across Heart Rate



Baseline vs. 320 mg: $p<0.05$ for all RR bins; Baseline vs. 160mg: $p<0.05$ for all RR bins;160 mg vs. 320 mg : $p=0.05$ for $RR \geq 750$ msec

Study 2

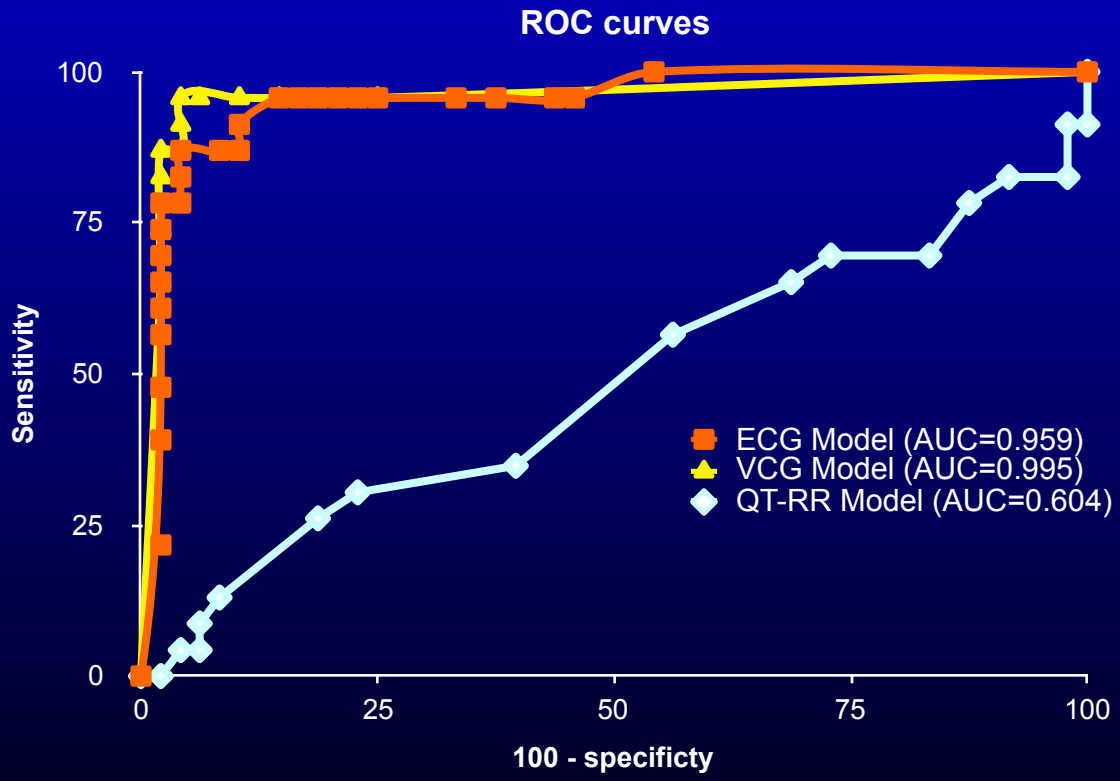
Scalar T-wave measurements, HR Dependency and LQTS Mutations



Healthy vs. LQT1: not significant for all RR bins; LQT2 vs. LQT1: $p<0.05$ for all RR bins

Study 2

Discrimination between LQT1 and LQT2 Patients



Model	Sens.	Spec.
Clinical	56%	57%
ECG	90%	91%
VCG	96%	96%

Sensitivity and specificity values based on optimal threshold of probability for being LQT2.

Conclusions

- The ECGs from LQTS patients show both a prolongation of the QT interval and abnormal T-wave morphology.
- Computerized method can help quantifying the morphology of the T-wave on scalar ECGs.
- We developed models suggesting that a measure of the T-wave morphology might be relevant for improving both the diagnosis of LQT2 patients and the identification of a patient mutations (LQT1 vs. LQT2).
- These preliminary results should be confirmed in an independent dataset.

What is the role of repolarization morphology in the acquired form of the LQTS?

Introduction

- **Most of the drugs remove form the market because of their cardiotoxic effect have been associated with a reduction of the rapid components of the potassium currents of the myocardial cells.**
- **The blockade of the rapid delayed-rectifier potassium currents (I_{Kr}) mainly prolongs the APD of the M-cells contributing to a profound changes in voltage gradient within the ventricles.** (1)

(1) Antzelevitch C, Shimizu W. Cellular mechanisms underlying the long QT syndrome. Curr.Opin.Cardiol 2002 Jan;17(1): 43-51
(2) Jurkiewicz NK, Sanguinetti MC. Rate-dependent prolongation of cardiac action potentials by a methanesulfonanilide class III antiarrhythmic agent. Specific block of rapidly activating delayed rectifier K+ current by dofetilide. Circ.Res. 1993 Jan;72(1):75-83

Working Hypothesis

- **We hypothesize that a reduction of the rapid components of the delayed-rectifier potassium current (I_{Kr}) is associated with abnormal static and dynamicity features of the T-wave.**

- **Based on two retrospective studies involving drug with I_{Kr}-kinetics inhibition, we investigated the abnormal electrocardiographic features of healthy individuals exposed to 2 drugs:**

  - **Study 3: what is the effect of sotalol on T-wave morphology?**
  - **Study 4: Is moxifloxacin associated with changes in T-wave morphology?**

Study 3

Sotalol Study

Study based on ECGs from Pfizer Inc. **Global Research and Development**

Sarapa N, Morganroth J, Couderc JP, Francom SF, Darpo B, Fleishaker JC, McEnroe JD, Chen WT, Zareba W, Moss AJ. Electrocardiographic identification of drug-induced QT prolongation: assessment by different recording and measurement methods. Ann.Noninvasive.Electrocardiol. 2004 Jan;9(1):48-57

Couderc JP, Zareba W, Moss AJ, Sarapa N, Morganroth J, Darpo B. Identification of sotalol-induced changes in repolarization with T wave area-based repolarization duration parameters. *J Electrocardiol* 2003;36 Suppl:115-20.

Couderc JP, Vaglio M, Xia X et al. Impaired T-amplitude adaptation to heart rate characterizes Ikr-inhibition in the congenital and acquired forms of the long-QT syndrome. Journal of Cardiovascular Electrophysiology. In press 2007.

Study Population

- Sotalol Study (Betapace®) :

✓ Holter ECGs were acquired for 3 days:
  - at baseline
  - after a single dose of sotatol (160 mg)
  - after a double dose of sotatol (320 mg)

– Thirty-nine healthy volunteers (11 females)
– Age: 18-45 yrs (mean 27 yrs)
– Weight: 47-108 kg (mean 74 kg)
– BMI: 18.2-30.8 kg/m^2 (mean 24.4 kg/m^2)
– 33 Caucasians, 2 Blacks, 2 unspecified

Holter ECG Recordings

-Ambulatory Holter ECGs:

- **-Holter H12 recorders providing 12-lead ECG signals (Mortara Instrument, Milwaukee, WI).**
- **-Amplitude resolution: 12 bits (6.25 μV)**
- **-Sampling frequency: 180Hz**
- **-ECG duration : ~24 hours**

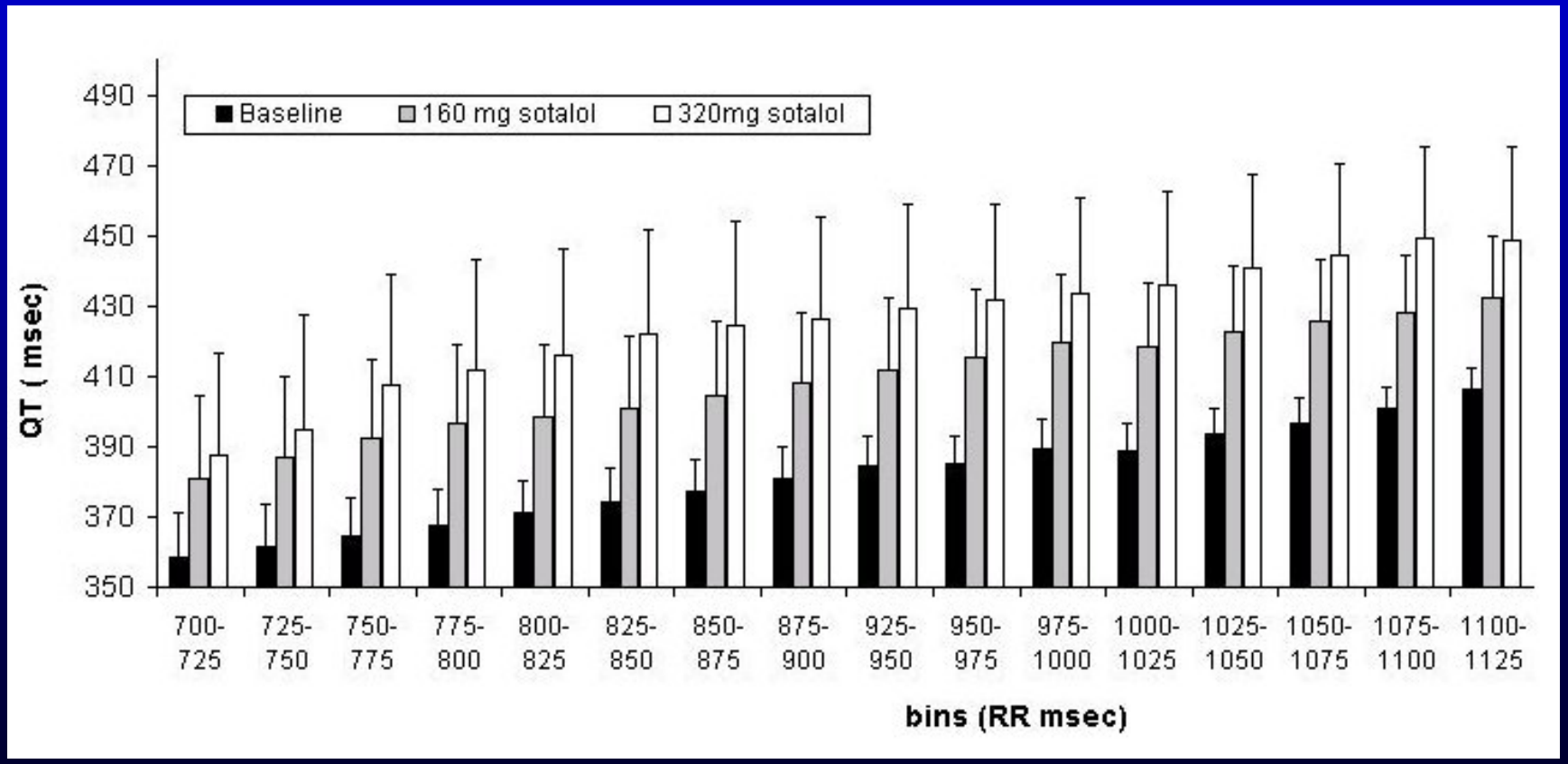
-Measurement during steady-state repolarization: Representative beats based on 10 consecutive beats.

- **-Steady state : ΔRR<300 msec within the preceding 5 minutes.**
- **-HR stability : |ΔRR|<10 %**
- **-Exclusion of on-sinus beats**

Study 3

Results

RR bin Analysis: QT



baseline vs. 320mg : $p<0.05$ for all RR bins
baseline vs. 160mg : $p<0.05$ for all RR bins
160 mg vs. 320 mg: $p=0.05$ for $RR \geq 750$ msec

Study 3

Results

ECG characteristics in the acquired LQTS

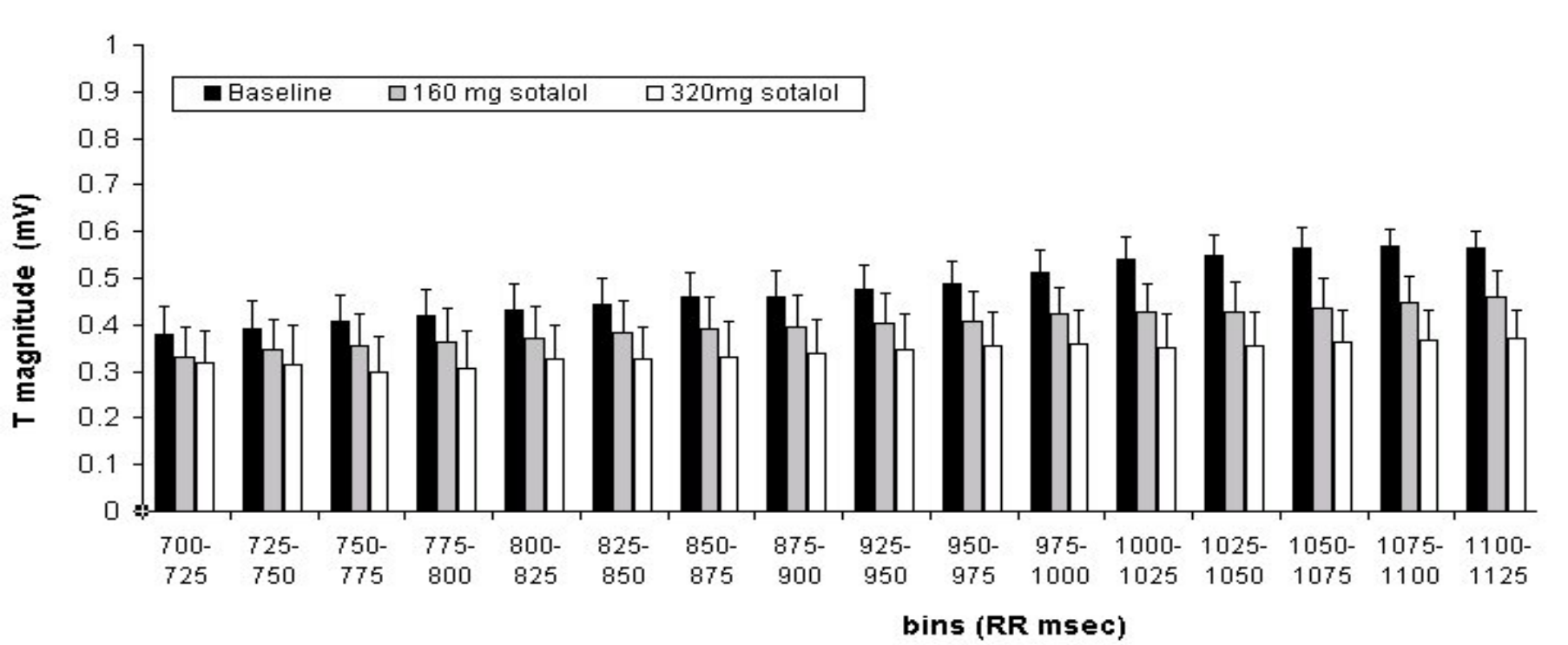
	Off drug n=37	Low dose n=37	High dose n=21
RR (ms)	784±72	893±63†	947±70†*
T-amplitude (mV)	041±0.15	0.41±0.15	0.36±0.12
QT (ms)	367±19	405±23†	427±24†*
QTc F (ms)	399±16	422±22†	437±20†*
QTc B (ms)	417±18	431±24†	441±20†

QTc B: QT corrected using Bazett's formula.
QTc F: QT corrected using Fridericia's formula.
†: $p < 0.01$ in comparison to off drug.
*** $p<0.05$ in reference to low dose group**

Study 3

Results

RR bin Analysis: T magnitude

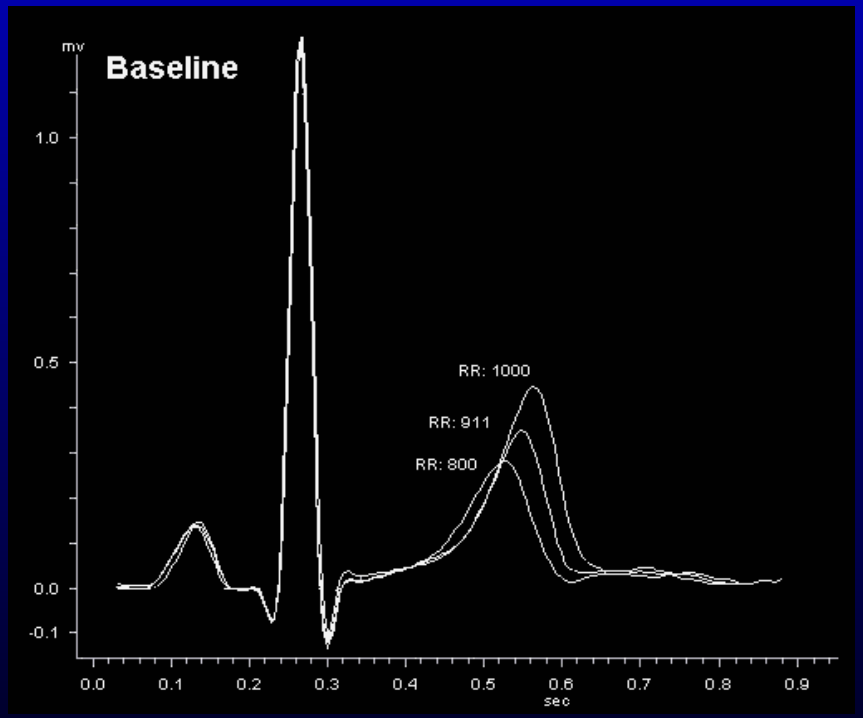


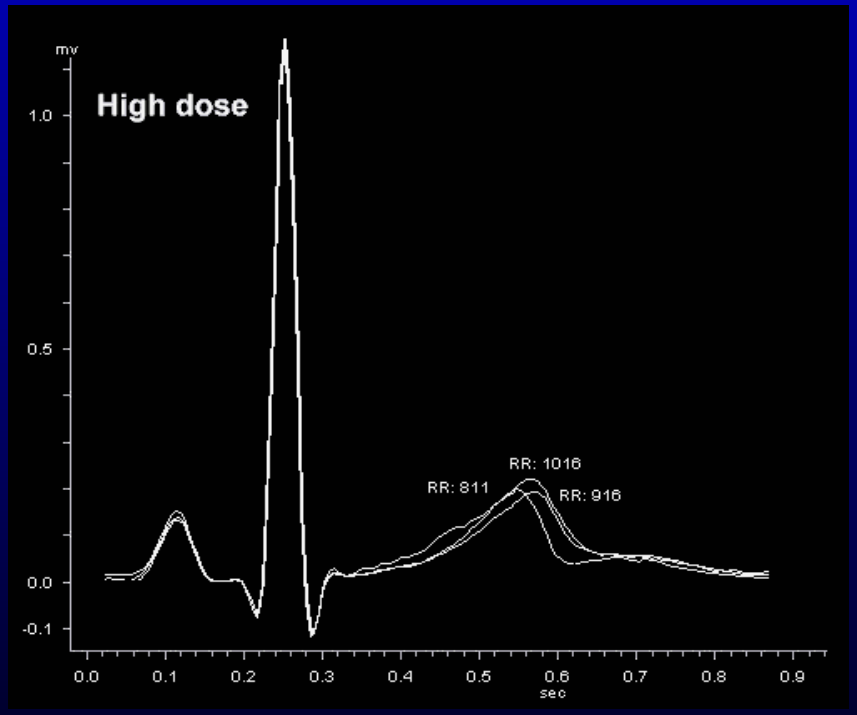
baseline vs. 320mg : $p<0.05$ for all RR bins
baseline vs. 160mg : $p<0.05$ for RR≥975 msec
160 mg vs. 320 mg: $p=0.06$ for RR≥1000 msec

Study 3

Results

T-wave amplitude impairment: ECG patterns





Study 2 & 3

Results

T-wave amplitude impairment as a I_{kr}-related abnormality

	Healthy N=37	LQT1 N=49	LQT2 N=25	Low dose Sotalol N=37	High dose Sotalol N=21
QT/RR slope (n.u.)	0.12±0.04	0.17±0.10*	0.22±0.16*	0.15±0.05*	0.14±0.06
Tamp/RR slope (μV/ms)	0.55±0.29	0.62±0.40	0.31±0.27*‡	0.26±0.19*‡	0.21±0.14*‡

* $p<0.05$ in reference to healthy, ‡ $p<0.05$ in reference to LQT1.

Study 2 & 3

Results

General linear mixed model : Predicting presence of sotalol

	OR	95% CI	p-value
QTc (1 msec inc.)	1.05	1.02-1.09	0.004
QT/RR slope (0.01 unit inc.)	1.16	0.98-1.10	NS
Tamp/RR slope (10μV/msec inc.)	0.54	0.36-0.82	0.005

OR: Odd Ratio, CI: confidence interval.
Adjusted for age and gender.

Study 4

Moxifloxacin Study

Pilot study based on data from the US-FDA ECG Warehouse

Couderc JP, McNitt S, Hyrien O et al. Electrocardiographic Abnormalities of Repolarization Induced by Moxifloxacin: Improving the Detection of Subtle IKr-Inhibition. Drug Safety J. In press 2007

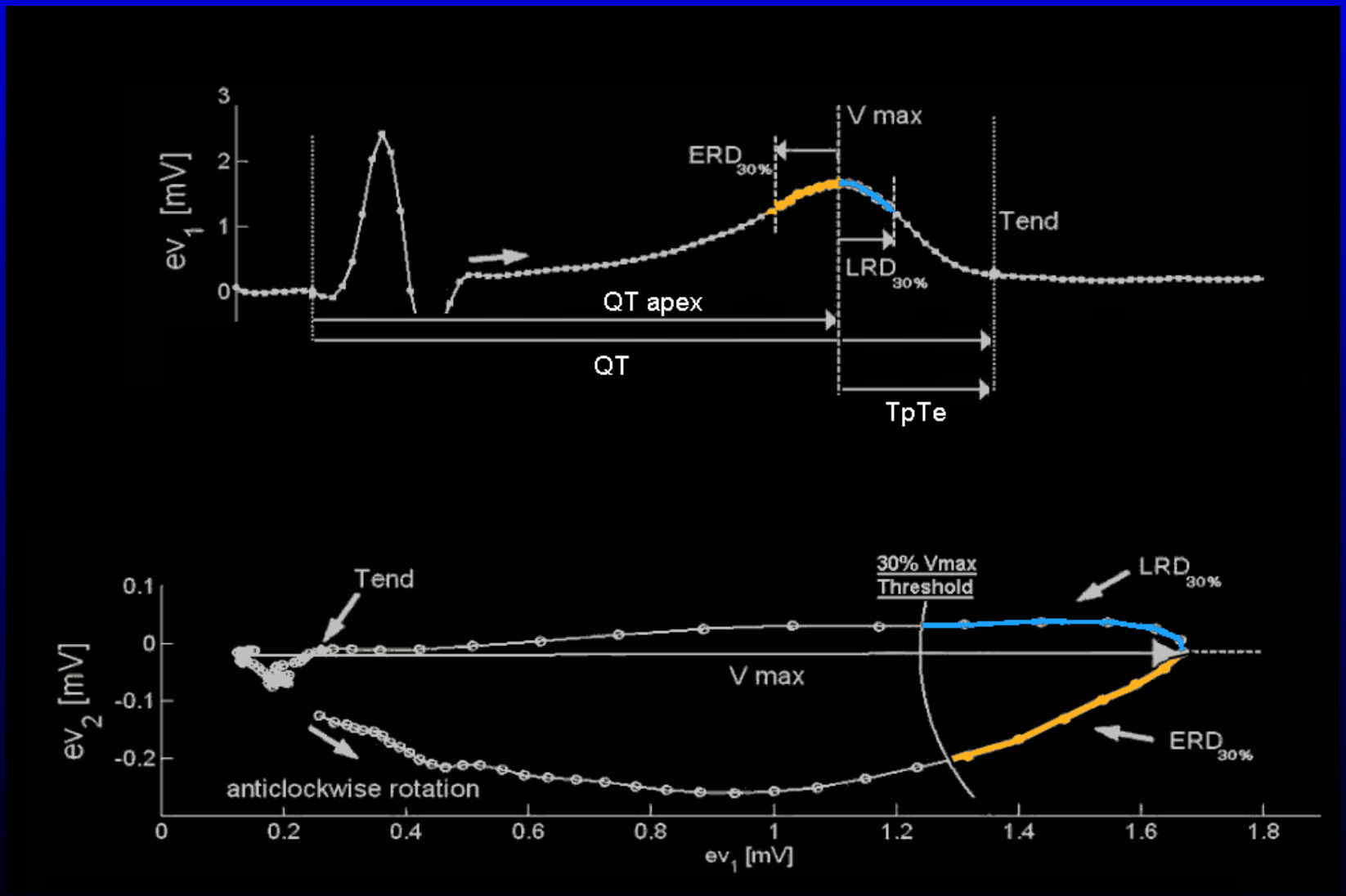
Couderc JP, Vaglio M, Xia X, McNitt S, Hyrien O. Electrocardiographic Method for Identifying Drug-induced Repolarization Abnormalities Associated with a Reduction of the Rapidly Activating Delayed Rectifier Potassium Current. IEEE Engineering in Medicine and Biology Society, New-York 2006 p. 4010-5.

Study Population

- Parallel design: 40 subjects, 18 females.
- Randomized, placebo-controlled study.
- 400 mg moxifloxacin.
- 160 Digital XML-FDA Standard 12-lead ECGs were extracted from the US-FDA warehouse.

Study 4

Repolarization Parameters



Study 4

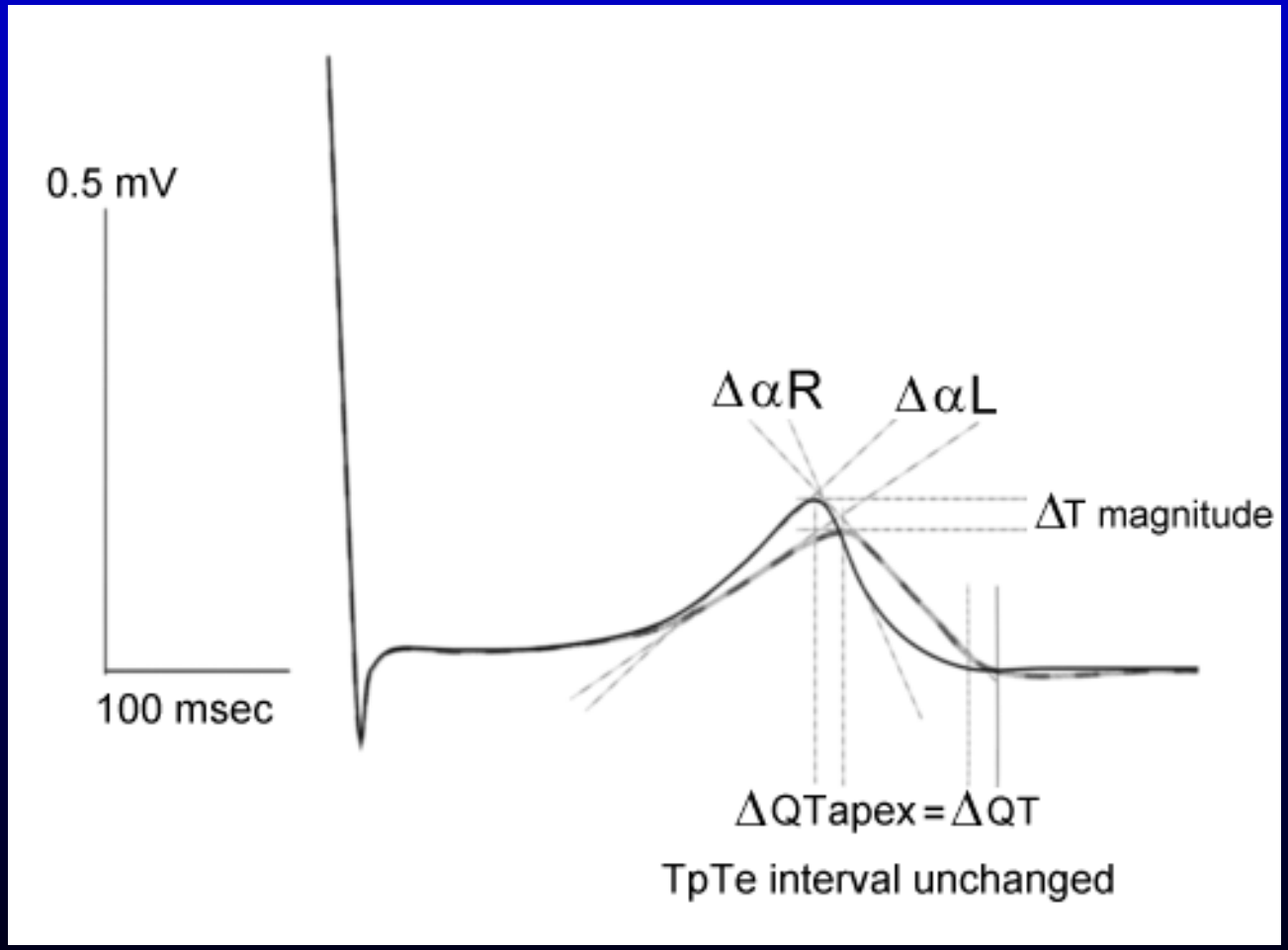
Analyses of Central Tendency

	Median difference vs. placebo	95% CI		p
		lower	Upper	
T magnitude (mV)	**-0.03**	**-0.05**	**0.00**	**0.08**
QT offset (msec)	**10**	**1.1**	**26.9**	**0.04**
αL (μV/ms)	**-0.3**	**-0.65**	**-0.07**	**0.03**
αR (μV/ms)	**0.4**	**0.08**	**1.08**	**0.06**
TpTe (msec)	0	-6.7	4.7	0.41
λ_2/λ_1	0.04	-0.1	0.1	0.41
$ERD_{30\%}$ (msec)	**14**	**3.8**	**18.4**	**0.01**

All measurements are corrected for HR using pooled-formula

Study 4

Moxifloxacin-induced Repolarization Abnormalities

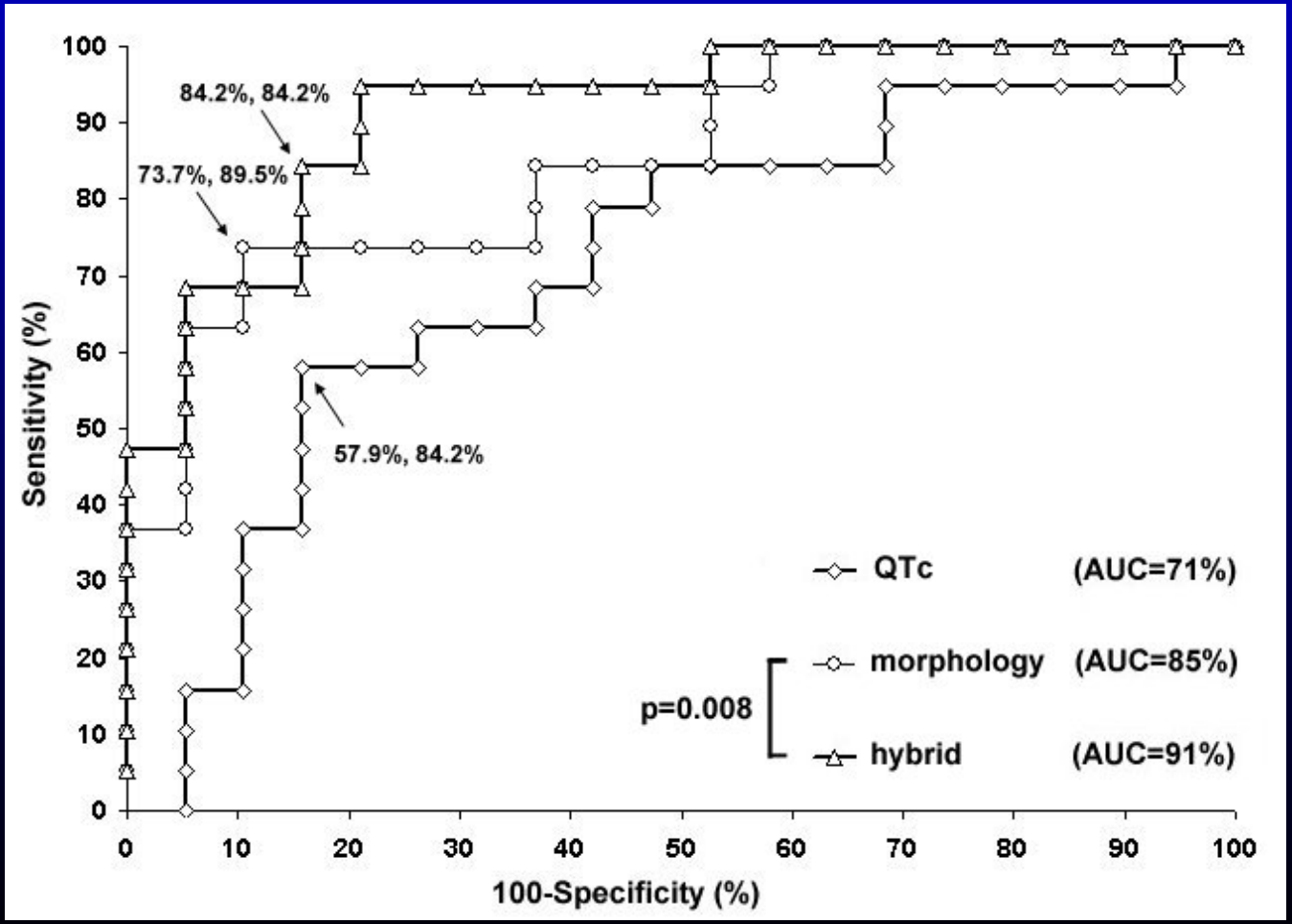


Simulated ECG tracings

Study 4

I_{kr}-related Repolarization Abnormalities from Surface ECGs Induced by Moxifloxacin

multivariate analysis



Study 4

Stability and Reproducibility

repolarization parameters

	Short term			Long term		
	IrPV	IaPV	Rep. (%)	IrPV	IaPV	Rep. (%)
QTc apex (msec)	17.9	10.0	76	17.0	12.1	67
QTc (msec)	17.0	12.0	68	12.1	20.7	**26**
TpTe (msec)	9.5	9.5	50	7.0	14.8	**18**
$LRD_{30\%}$ (msec)	4.9	4.0	60	5.4	4.0	64
$ERD_{30\%}$ (msec)	10.5	5.6	77	7.3	8.4	43
T amplitude (mV)	0.05	0.03	74	0.04	0.03	63
αL (μV/ms)	0.52	0.35	69	0.46	0.41	55
αR (μV/ms)	0.87	0.58	69	0.71	0.62	57
Complexity (λ 2/ λ 1)	0.03	0.07	**14**	0.07	0.06	57
Planarity (λ3)	0.01	0.02	**33**	0.02	0.01	82

IrPV: Inter-patient variability
IaPV: Intra-patient variability
Rep.: Reproducibility based on ICC value.
Values in bold highlights the repolarization parameters with poor level of reproducibility (<40%)

Conclusions

Static and dynamic repolarization morphology is significantly altered by moxifloxacin and sotalol , drugs inhibiting the IKr current. A computerized ECG technique f quantifies morphological changes of repolarization segment.

In these preliminary studies, our new parameters reflecting morphology of T wave provided better identification of the presence of drug-induced Ikr blockade in healthy individuals than the QTc interval.

Is There a link between Abnormal Repolarization Morphology and Torsades de Pointes?

- **Study 5: Do patients with an history of torsades de pointes carry specific repolarization abnormalities ?**

Couderc JP, Kaab, S Hionterseer M et al.: Baseline Values and Drug-induced Changes of the Ventricular Repolarization Morphology in the Electrocardiograms of Patients with a History of Drug-induced Torsades de Pointes. Circulation (supplement), 2007, (in press)

Study Populations I

The patients were enrolled after being admitted to the University Hospital, Munich for documented TdPs in the context of a drug with QT-prolonging potential. A group of (N=17) individuals matched for gender and age were used as reference group.

The patients were all genetically tested for presence of mutation of the major LQTS genes using standard genotyping techniques (genomic DNA was prepared from lymphocytes, amplification of KCNQ1, KCNH2, KCNE1, KCNE2 and SCN5A using polymerase chain reactions were performed, followed by direct sequencing of these major LQT-disease genes).

Study 5

Results

	Baseline (absolute values)			Sotalol challenge (sotalol induced changes)		
	(-) TdPs N=17	(+) TdPs N=16	P values	(-) TdPs N=17	(+) TdPs N=16	P values
QTc apex	340±24	347±35	0.53	*54(37)±24**	*75(53)±37**	*0.06*
QTc	*435±32*	*461±45*	*0.07*	**55(61)±27***	**94(103)±46***	**0.01**
TpTe	108 ±35	108 ±31	0.74	**6(7)±20**	**36 (25)±41***	**0.01**
ERD30% (msec)	**35 ±8**	**44 ±13**	**0.02**	15 ±19*	12 ±20*	0.68
ERD50% (msec)	**57 ±13**	**71 ±22**	**0.03**	26 ±30*	28 ±28*	0.82
ERD70% (msec)	91±32	112±40	0.09	33±44*	36±51*	0.86
LRD30% (msec)	28 ±5	35 ±17	0.12	6 ±10	6.±15	0.93
LRD50% (msec)	43 ±5	55± 32	0.14	*7 ±10**	*21 ±27**	*0.07*
LRD70% (msec)	*66 ±11*	*86 ±44*	*0.08*	**8(9)±13**	**27(28) ±30***	**0.03**

Conclusions

It is important for clinicians and for pharmaceutical companies to be able to assess the level of predisposition to TdPs of individuals. Our results revealed that there are specific repolarization changes at baseline and on sotalol challenge in patients with history of TdPs. This information could help optimizing therapeutic strategies for cardiologists and improve design of studies for drug-safety assessment.

Main Conclusions

- **Our work demonstrates the presence of static and dynamic abnormalities of the repolarization segment in individuals exposed to I_{Kr}-inhibiting compounds in the congenital and acquired form of the LQTS.**

- **Based on quantitative electrocardiographic parameters, we were able to measured these changes. Our studies suggest that the repolarization morphology brings relevant information for:**
  - **Identifying type of LQTS mutation**
  - **Complement QT prolongation for diagnosis of the LQT2**
  - **Improve the detection of drug-induced Ikr blockade from surface ECGs.**
  - **Reveal abnormal ECG pattern in patients with a history of drug-induced torsades de pointes.**

- **These results are preliminary but these ECG markers may play an important role in the future of assessment of the I_{kr}-related cardiotoxicity of drugs.**

Acknowledgments

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- **Dr. Norman Stockbridge, Michael Li: US-FDA CDER, DC, USA**
- **Drs. Stefan Kaab, Martin Hinterseer, Britt-M. Beckmann Ludwig-Maximilians-University, Munich, Klinikum Grosshadern, Department of Medicine 1, Munich, Germany**
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